Preclinical studies of a new potent orally active antagonist for the MIF-CD74 axis in development for pulmonary hypertension.

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Background – We have recently identified that macrophage migration inhibitory factor (MIF) and its signaling through CD74 are key players at the crossroad of inflammation, cancer-like phenotype and endothelial dysfunction in the pathogenesis of pulmonary hypertension (PH). Although several classes of small molecule MIF inhibitors have been described in the literature, none have yet been approved for clinical use. Therefore, we have designed and synthesized a new potent orally active antagonist, N-(phenylmethyl)benzoxazol-2-thione MFC-1040, and herein we investigate its chronic pharmacological effect in PH in vitro and in vivo.

Methods and Results – We have used an integrated approach to screen 26 new bioactive compounds for their ability to attenuate DU-145 cell survival, a human cancer cell line that requires MIF-CD74 activated signal transduction pathways for their cell survival. The best response was achieved with the N-(phenylmethyl)-benzoxazol-2-thione MFC-1040, an observation that was replicated in vitro, with cultured pulmonary endothelial cells (ECs) from patients idiopathic PH exhibiting diminished sensitivity to apoptotic induction. Interestingly, we found a beneficial curative effect of chronic treatment with N-(phenylmethyl)-benzoxazol-2-thione MFC-1040 in two pre-clinical models of severe PH, namely monocrotaline (MCT) and the SU5416-hypoxia (SuHx) rat models. Compound MFC-1040 showed significant protective effect against PH as it delayed disease progression, decreased values of mean pulmonary arterial pressure, pulmonary vascular resistance, degree of pulmonary vascular remodelling and reversed right ventricular hypertrophy.

Conclusion – Our study demonstrates the in vitro and in vivo efficacy of N-(phenylmethyl)-benzoxazol-2-thione MFC-1040, a new orally bioavailable MIF/CD74 antagonist. Additional optimization of activity and drug properties of this compound are ongoing.

Keywords: Inflammation; Pulmonary vascular remodelling; Cell survival; Macrophage migration inhibitory factor; CD74; Therapeutic innovation.